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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

TECH CENTER 1600/2900

Applicant: Tullis, *et al.*

Serial No.: 09/917,138

Confirmation No: 4876

Filed: July 26, 2001

For: **ENZYMATIC LABELING AND
DETECTION OF DNA
HYBRIDIZATION PROBES**

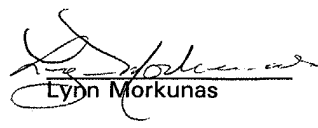
Art Unit: 1655

Examiner: Unassigned

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Assistant Commissioner for Patents
Washington, D.C. 20231, on this date.

02/08/02
Date


Lynn Morkunas

TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is a Preliminary Amendment for filing with the above-referenced application.

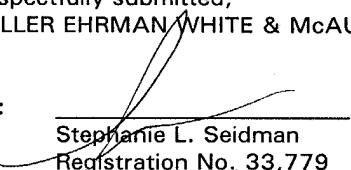
(X)

The Commissioner is hereby authorized to charge any fees that may be due under 37 C.F.R. §§1.16-1.17 in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-1213. A duplicate of this sheet is enclosed.

* * *

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By:


Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 24730-2207B

Address all correspondence to:

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HELLER EHRMAN WHITE & McAULIFFE LLP

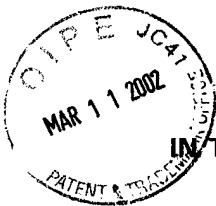
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E. Williams
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02/8/02
Date

Lynn Morkunas
Lynn Morkunas

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to the examination of the above-captioned application,
please amend the application as follows:

IN THE SPECIFICATION:

Please amend the specification as follows (a marked up copy of the
amended specification is attached to this Amendment):

Please replace the paragraph on page 1, line 18, to line 22, with the
following paragraph.

AI
DNA probes and primers have found a variety of commercial and research
applications in DNA hybridization diagnostics including DNA and RNA target
amplification technologies (PCR, LCR and NASBA); signal amplification
technologies such as branched DNA probes, dendrimers and the like; and direct
DNA probes for less sensitive detection.

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Please replace the paragraph on page 3, line 22, to page 4 line 13, with the following paragraph.

A2
Another system that has been applied to genotyping is the Taqman system (Perkin Elmer, Foster City, CA). In the Taqman paradigm (see, *e.g.*, Holland *et al.* (1991) *Proc. Natl. Acad. Sci. U.S.A.* 88:7276-7280), fluorescent energy-transfer probes known as Taqman probes or Molecular Beacons have been employed in a homogeneous format to detect amplification products. A Taqman probe includes a fluorescent donor and fluorescent quencher typically attached to the 3' and 5' ends of a sequence specific oligonucleotide (SSO). In a Molecular Beacon, the quencher is a non-fluorescent chromophore, such as, but are not limited to, DABCYL (4-(4-dimethylaminophenyl)azobenzoic acid; see, *e.g.*, Kostrikis *et al.* (1996) *Science* 279:1228-1229) and EDANS (5-((2-amino-ethyl)amino)-naphthalene-1-sulfonic acid), which is fluorescent group quenched by the DABCYL group. During amplification, the exonuclease activity of Taq polymerase cleaves the probe between the quencher and the fluor, causing a directly observable increase in fluorescence of from 3-20 fold. The Taqman system combines the amplification and detection in a closed system reducing the risk of contamination and allowing multiplex detection. There are drawbacks to this system. Taqman probes vary substantially in quenching efficiency and are difficult to synthesize and purify. As a result, the system tends to be less robust than typical clinical systems and cannot use highly modified DNA probes that are resistant to nucleases. Moreover, Taqman probes and the associated instrumentation to detect fluorescence changes can be quite expensive.

Please replace the paragraph on page 6, line 29, to page 7 line 11, with the following paragraph.

A3
As used herein, a non-template dependent chain extending enzyme refers to template independent polymerases capable of adding polynucleotide tails to

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A.3
Cont'd

the termini of DNA or RNA molecules. Chain extending enzymes include, but are not limited to, telomerases such as terminal transferases, that are capable of producing extended polynucleotide tails. Telomerases extend the 3' termini of chromosomes thereby stabilizing chromosomal structure. Assays to identify telomerases are known (see, *e.g.*, U.S. Patent Nos 5,489,508; 5,645,986 and 5,648,215). Generally telomerase activity is measured by primer chain elongation under conditions that minimize interference from other genomic sequences. For example, U.S. Patent No. 5,629,154 describes telomerase activity assays. In these assays, telomerase activity in a sample is measured using a two reaction protocol involving telomerase substrate and primer extension steps.

Please replace the paragraph on page 14, line 7, to line 19, with the following paragraph.

A4

The products of the chain extension reaction can then be detected by suitable methods known to those of skill in the art. Such methods include, but are not limited to:

- 1) Direct luminescent detection via incorporated fluorescence or chemiluminescent nucleoside triphosphates.
- 2) Indirect fluorescence or chemiluminescence mediated by antibodies, streptavidin or other lectins or aptamers
- 3) Enzymatic reporter groups attached to antibodies, streptavidin or other lectins or aptamers
- 4) Up converting phosphors or fluorescent beads attached to oligomers.

Hence, suitable labels include any detectable label that can be incorporated into an extended chain.

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IN THE CLAIMS:

Please replace Claims 1 and 10 with amended Claims 1 and 10 as follows:

- A4
1. A method, comprising:
 - a) treating nucleic acid molecules or modified nucleic acids in a sample with a reagent or reagents that render the nucleic acid chains unextendable by a non-template-dependent enzyme; and
 - b) hybridizing the treated molecules with a nucleic acid probe that includes an extendable terminus, under conditions whereby hybrids form; and
 - c) treating any hybrids formed with a non-template dependent chain elongating enzyme and substrates therefor, whereby any hybridized probe is extended.

- A5
10. The method of claim 9, wherein the telomerase is terminal deoxynucleotidyl transferase.

REMARKS

The amendments to the specification and Claim 1 rectify minor typographical errors. The amendment to Claims 10 corrects an error in claim dependency. Therefore, no new matter has been added.

It is believed that no fee is due. However, if it is determined that a fee is due, any fees that may be due in connection with this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213.

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TULLIS, *et al.*
PRELIMINARY AMENDMENT

In view of the amendments and above remarks, entry of the amendments and examination of the application on the merits are respectfully requested.

* * *

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____

Stephanie Seidman
Registration No. 33, 779

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